PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P34922WO/NCB	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 03/05035	International filing date *(day/month/year)* 18.11.2003	Priority date *(day/month/year)* 18.11.2002
International Patent Classification (IPC) or both national classification and IPC C07C317/44		
Applicant QUEEN MARY & WESTFIELD COLLEGE et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01.06.2004	17.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer English, R Telephone No. +31 70 340-2860

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/05035

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-68 as originally filed

Claims, Numbers

1-33 as originally filed

Drawings, Sheets

1-6 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-3,8-18,29,30(in part), 31,32

   because:

   ☒ the said international application, or the said claims Nos. 31,32 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-3,8-18,29-31 (in part)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4,5,7,10,17,18,20,23-25,27,28,32,33
	No:	Claims	1-3,6,8,9,11-16,19,21,22,26,29-31
Inventive step (IS)	Yes:	Claims	4,5,7,10,17,18,32,33
	No:	Claims	1-3,6,8,9,11-16,19-31
Industrial applicability (IA)	Yes:	Claims	1-30,33
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The International Search Report was incomplete with respect to a part of the subject-matter of claims 1-3,8-18,29-31. It was complete only for the compounds of claims 4-7,18-20 and the examples relating to compounds of formula (I) as well as the use of compounds of claims 1,20 for the inhibition of histone deacetylase (HDAC) and the treatment of the diseases listed in claim 33. Consequently, it is not possible to carry out a full International Preliminary Examination of claims 1-3,8-18,29-31 (Article 66.1(e) PCT).

2. Claims 31,32 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: G.X. Ma, et al., Synthetic Communications, 1997, 27(14), 2445-2453 (XP008028581)
D2: GB 2 101 600 (Montedison) 19 January 1983
D3: Q.B. Cass, et al., Journal of the Chemical Society, Perkin Transactions 1, 1991, (11), 2683-2686 (XP002273305)
D4: T.A. Gourdie, et al., Journal of Medicinal Chemistry, 1990, 33(4), 1177-1186 (XP002273306)
D5: I. Flemming, et al., Tetrahedron Letters, 1979, (34), 3205-3208 (XP002273307)
D6: G. Cai, et al., Journal of the American Chemical Society, 1993, 115(16), 7192-7198 (XP000673163)
D7: A.G.M. Barrett, et al., Journal of Organic Chemistry, 1986, 51(25), 4840-4856 (XP002273308)

D8: R.A. Bunce, et al., Journal of Organic Chemistry, 1993, 58(25), 7143-7148 (XP002273309)

D9: US 4 013 776 (V. Lafon) 22 March 1977

D10: A.S. Kalgutkar, et al., Journal of Medicinal Chemistry, 1998, 41(24), 4800-4818 (XP002273310)

D11: M. Cowart, et al., Journal of Medicinal Chemistry, 19980, 41(14), 2636-2642 (XP002273311)

D12: G. Dannhardt, et al., Die Pharmazie, 1997, 52(6), 428-436 (XP002273312)

D13: M. Yoshida, et al., Journal of Biological Chemistry, 1990, 265(28), 17174-17179 (XP000616087)

3. **Subject-matter**

The present application discloses certain sulphur-containing compounds (claims 1-19), processes for their preparation (claims 21-28) and their use as inhibitors of HDAC (claims 29-33). In particular, these compounds consist of an R^1-S(=Y)-CHR^2 group attached via a saturated or unsaturated C_2-C_{13} carbon chain optionally containing rings to a C(=O)-X group, where X is an OR, NHR, NROR, NRNHR or SR group and R is a hydrogen atom or an alkyl group.

Also claimed is the compound 4-(4-dimethylaminophenylsulphanyl)-2-methyl-2-penten-1-ol (claim 20).

4 **Novelty**

4.1 The present application does not meet the requirements of Article 33(2) PCT, because the subject-matter of claims 1-3,6,8,9,11-16,19,21,22,26,29-31 is not new. As noted in paragraph 1 above, a large number of documents was revealed during the International Search relevant to the novelty of claim 1 and many of the claims dependent upon it and some of these were cited in the International Search Report. **This cannot be regarded as a complete list of documents in the prior art dealing with compounds of claim 1.**

Thus, documents D1-12 each describe at least one compound falling within the scope of claim 1 (see International Search Report for details) and D10-D12 also indicate that the relevant compounds therein have pharmaceutical use (claims 29-31).

In particular, document D3 describes methyl 6-(phenylsulphinyl)hexa-2E,4E-dienoate (compound 16) which is a compound of claim 1 in which R_1 is phenyl, Y is 1 oxygen atom, n is 1, the dotted line represents a double bond, R_2 and R_3 are hydrogen atoms, Q is a CH=CH group and X is a methoxycarbonyl group. Indeed, this compound is the same compound as example 8a of the present application.

Document D4 describes methyl 6-[(4-aminophenyl)thio]hexanoate (compound 25c) which is a compound of claim 1 in which R_1 is 4-aminophenyl, Y is "0 oxygen atoms", n is 1, the dotted line represents a single bond, R_2 and R_3 are hydrogen atoms, Q is a CH_2-CH_2 group and X is a methoxycarbonyl group. Indeed, this compound is the same as the compound of example 28d of the present application.

4.2 No prior-art documents describing 4-(4-dimethylaminophenylsulphanyl)-2-methyl-2-penten-1-ol have been revealed. Consequently, the subject-matter of claim 20 appears to be novel and to satisfy the requirements of Article 33(3) PCT.

4.3 Document D13 discloses trichostatin A (7-[4-(Dimethylamino)phenyl]-N-hydroxy-4,6-dimethyl-7-oxo-2,4-heptadienamide) as an inhibitor of mammalian HDAC. This prior- art compound differs from those of the present application in that it has a carbonyl group in place of the sulphur atom or sulphur-containing group of the latter. The use of the compounds of claim 1 as inhibitors of HDAC or in the treatment of the diseases listed in claim 33 is not disclosed in D13 or anywhere else in the prior art. Consequently, the subject-matter of claims 32,33 appears to be novel and to satisfy the requirements of Article 33(2) PCT.

5. **Inventive step**

5.1 Document D13, which is considered to represent the most relevant state of the art to the subject-matter of claims 1-19,29-33 (in so far as they are novel), discloses trichostatin A as an inhibitor of mammalian HDAC (see paragraph 4.3 above). Trichostatin A differs from the subject-matter of claims 1-19,29-33 in that the compound contains a carbonyl group in place of the sulphur atom or sulphur-containing group of the HDAC inhibitors of the present application.

The compounds of the present invention appear to be less active than trichostatin A in inhibiting HDAC (tables 1,2 on pages 67,68), but have been shown to be more

metabolically stable (page 68, lines 12-18). The problem to be solved by the claims 1-19,29-33 of the present application may therefore be regarded as the provision of improved inhibitors of HDAC. The applicant solves this problem by the use of the compounds of claim 1.

There is nothing in D13, or anywhere else in the prior art, to suggest that replacing the carbonyl group of trichostatin A with a sulphur atom or sulphur-containing group would lead to HDAC inhibitors with greater metabolic stability. Consequently, the subject-matter of claims 1-19,29-33, in so far as it is novel, appears to involve an inventive step and to meet the requirements of Article 33(3) PCT.

5.2 The compound 22b of claim 20 is not a compound of general formula (I) and so dees not fall within the scope claims 29-33. However, it is implied on page 19, lines 11-16 that this compound is intended to be an inhibitor of HDAC of the present invention and not merely an intermediate in the synthetic process in the preparation of compounds 24c and 25c (pages 49-50).

Compound 22b differs from the prior art compound of D13 in that the carbonyl group of the latter has been replaced by a sulphur atom, the hydroxyiminocarbonyl group of the latter has been reduced to a hydroxymethyl group and a $CH_2=CH_2$ group has been removed.

No pharmacological data is presented in the present application for this compound so it is not possible to determine what technical effect is of using this compound in place of trichostatin A in the inhibition of HDAC. The problem to be solved by present claim 20 may therefore be regarded as the provision of an alternative compound which inhibits HDAC. The applicant solves this problem by means of compound 22b.

There is nothing in D12,D13 or any where else in the prior art to suggest that making the structural changes to trichostatin A mentioned above would result in a compound that would inhibit HDAC. However, in the absence of any pharmacological data for compound 22b which demonstrates that it does indeed solve the problem posed, an inventive step cannot be acknowledged for the subject-matter of claim 20 and the requirements of Article 33(3) PCT do not appear to be met.

5.3 Claims 21-28 concern processes for the preparation of compounds of formula (I), many of which are not novel, either by coupling of a thiol with a suitable compound bearing a leaving group or by coupling of phosphorus reagents with aldehydes. These methods appear to be normal in the art. Consequently, the subject-matter of claims 21-28 does not appear to involve an inventive step and does not satisfy the requirements of Article 33(3) PCT.

However, in so far as the products of formula (I) are novel and inventive, any process for preparing them can also be considered as being inventive (Article 33(3) PCT).

6. **Industrial applicability**

For the assessment of the present claims 31,32 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognise as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.